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Original Article

Cumulative total S-1 dose in adjuvant chemotherapy affects the long-term outcome following curative gastrectomy for gastric cancer

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Abstract: A recent JCOG1104, OPAS-1 trial revealed the significance of S-1 duration. However, the significance of cumulative total S-1 dose (CTSD) remains unclear. In this study, we designed to evaluate the prognostic effect of CTSD on adjuvant chemotherapy after curative gastrectomy. We retrospectively analyzed 77 consecutive pStage II and III gastric cancer (GC) patients, who underwent curative gastrectomy followed by adjuvant S-1 chemotherapy from 2008 through 2014. CTSD of 20000 mg was the upper-limit of cut-off value to stratify the prognosis (5-year relapse free survival (RFS); CTSD < 20000 mg vs. CTSD ≥ 20000 mg: 51.9% vs. 85.1%, $P = 0.004$). Compared patients with CTSD more than 20000 mg, those with CTSD less than 20000 mg had a significantly higher rate of preoperative anemia ($P = 0.041$), low nutrition ($P = 0.008$) and open gastrectomy ($P = 0.012$). Multivariate Cox's proportional hazards model for RFS proved that CTSD less than 20000 mg was an independent prognostic factor [$P = 0.031$, HR 3.32 (95% CI: 1.11-11.1)] although S-1 intensity and duration were not independent prognostic factors. The cumulative total S-1 dose more than 20000 mg might contribute to better prognosis.

Keywords: Gastric cancer, prognosis, adjuvant chemotherapy

Introduction

Gastric cancer (GC) is fifth most common cause of cancer-related death worldwide [1]. Perioperative management techniques, surgical techniques and chemotherapy regimens have critically improved [2-4]. Nevertheless, GC remains one of the aggressive gastrointestinal cancers. Curative gastrectomy with lymph node dissection has been recognized as the opportunity for macroscopic tumor clearance. However, the surgical resection was considered to be effective for only local control of the primary tumor [2, 3, 5, 6], hence, recurrence due to micrometastasis cannot be prevented. Therefore, adjuvant chemotherapy has been recommended to achieve microscopic tumor clearance of advanced GC [7].

The ACTS-GC trial and the CLASSIC trial, phase 3 trials, revealed the efficacy of adjuvant chemotherapy for pStage II and III GC compared to surgery alone. The ACTS-GC trial showed that S-1 is recommended as standard adjuvant chemotherapy for pStage II or III GC patients after curative gastrectomy to improve prognosis [8, 9]. Moreover, a recent JCOG1104 (OPAS-1) trial revealed that S-1 for one year should remain as the standard adjuvant chemotherapy for GC patients with pStage II. This trial was stopped early because the hazard ratio (HR) for RFS of the four-course group compared to the eight-course group exceeded the pre-specified stopping criteria and was unlikely to indicate non-inferiority. However, the updated 3-year RFS was 89.8% for the 4-course group and 93.1% for the 8-course group (HR 1.84, 95% CI 0.93-3.63) [10]. This study suggested the cumulative S-1 dose of 6 months might be inferior to that of 12 months form viewpoints of prognosis.

There are uncertainties about the effects of total S-1 dose and how to increase it, although the timing and duration of S-1 administration after surgery have been investigated [10-13]. It has been reported that S-1 monotherapy by oncolo-

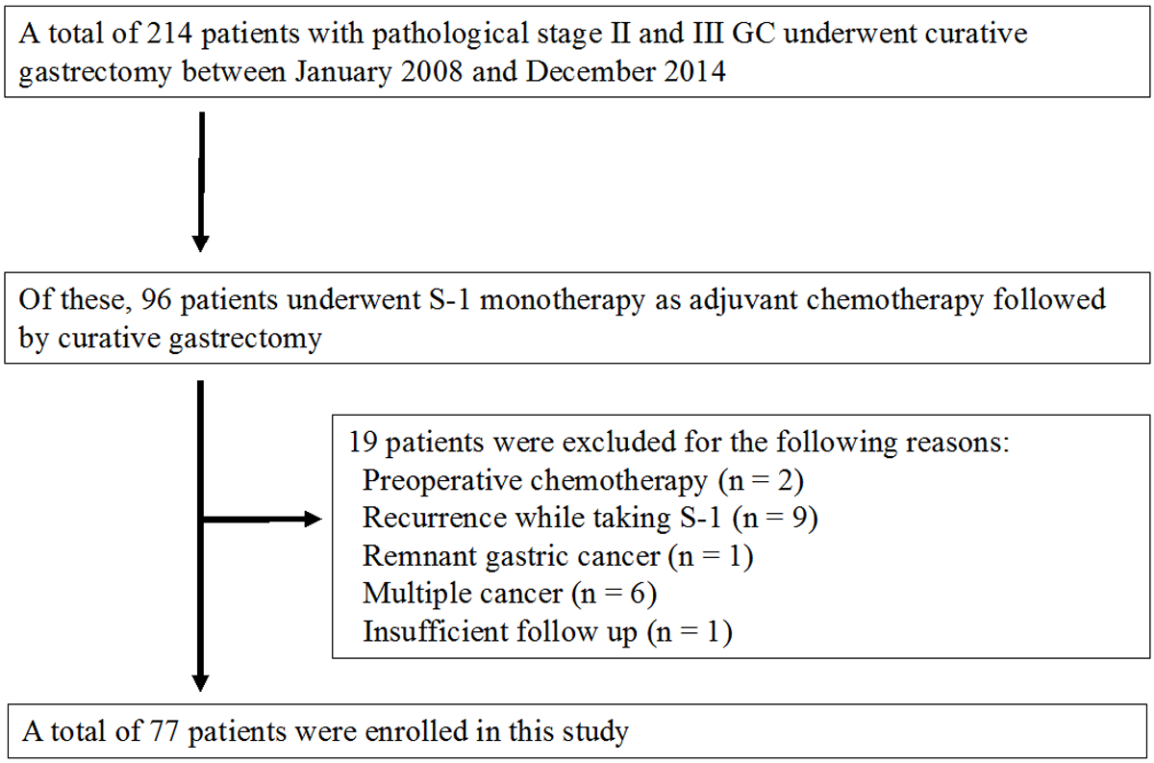


Figure 1. Patients enrolled in this study. A total of 96 patients with pathological stage II and III GC underwent curative gastrectomy and adjuvant S-1 monotherapy between January 2008 and December 2014. Of these, 19 patients were excluded from this study for the reasons listed in the main text. Consequently, a total of 77 patients were enrolled in this study.

gists achieved a higher completion rate than by surgeons in patients aged 65 and over. The reason is that S-1 monotherapy is more often managed by oncologists than surgeons, including suspensions or delays, changes in schedule, and dose modifications [14]. It is important to administer S-1 while controlling for side effects, and the cumulative total S-1 dose including the S-1 intensity and duration may be the key to S-1 monotherapy.

In this study, we hypothesized that the optimal cumulative total S-1 dose (CTSD) could be more pivotal prognostic factor than the S-1 intensity and duration. To verify this hypothesis, we compared the prognostic effects of CTSD, the S-1 duration and the S-1 dose intensity in adjuvant chemotherapy for GC. The results of our study may provide evidence that the cumulative total S-1 dose might affect the prognosis strongly.

Materials and methods

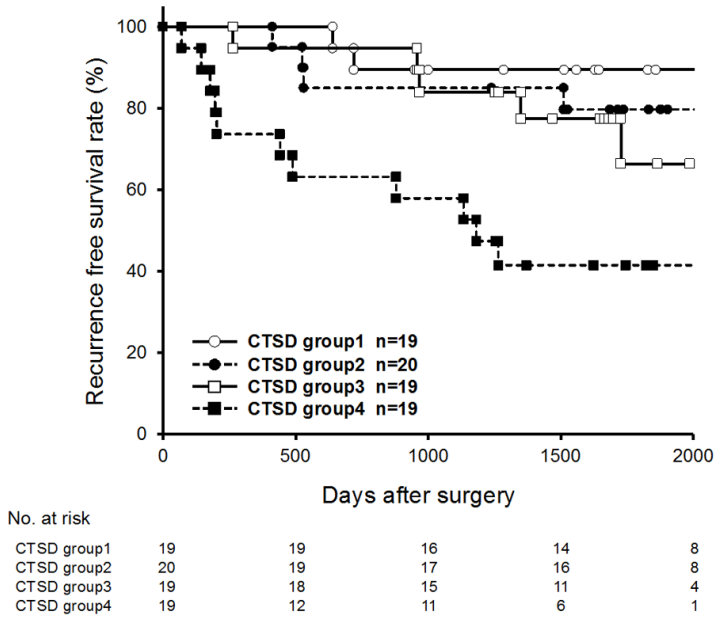
Study population

We retrospectively analyzed 214 consecutive pStage II and III GC patients who underwent curative gastrectomy at the Division of Digestive Surgery, Kyoto Prefectural University of Medicine. Of these, 96 patients underwent adjuvant S-1 monotherapy from 2008 through 2014. The lymphadenectomy was done depending on the tumor location and the clinical stage defined by the Japanese classification of gastric carcinoma (JCGC) [15, 16].

Of these 96 patients, 19 patients were excluded from this study for multiple cancer (n = 6), preoperative chemotherapy (n = 2), recurrence while taking S-1 (n = 9), remnant gastric cancer (n = 1) and insufficient follow up (n = 1). Consequently, 77 patients were enrolled in this study. The resected specimens were examined by at least two pathologists, and evaluated based on the 15th JCGC [17] and 8th UICC staging system [18] (**Figure 1**).

Evaluation of the cumulative total S-1 dose (CTSD), intensity and duration

Firstly, the total S-1 dose was calculated the following formula: the total S-1 dose = S-1 dose (mg) x duration (days). Next, CTSD was calculated based on the patients of body surface



No. at risk

CTSD group1	19	19	16	14	8
CTSD group2	20	19	17	16	8
CTSD group3	19	18	15	11	4
CTSD group4	19	12	11	6	1

Figure 2. Relapse-free survival analysis of each group divided according to CTSD. CTSD was divided into 4 groups from the top (group 1: 26640-93520 mg, group 2: 20571-26320 mg, group 3: 9520-20533 mg, group 4: -9333 mg) and able to stratify prognosis.

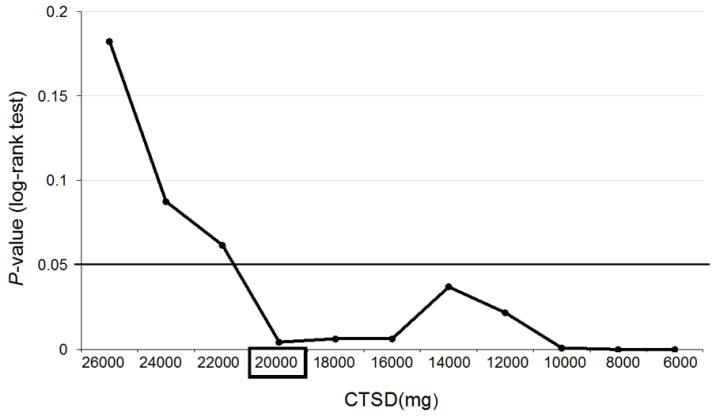


Figure 3. Cutoff values of CTSD to stratify the prognosis in pStage II and III gastric cancer. Survival analyses was performed using various cutoff values 6000 mg to 26000 mg. The cut-off value of 20000 mg was the upper limit of cut-off value to stratify the prognosis.

area (BSA) more than 1.5 m^2, the patients of BSA less than 1.25 m^2 is 1.25 times the total S-1 dose and the patients of BSA from 1.25 m^2 to 1.5 m^2 is 1.25 times. First of all, CTSD was divided into 4 groups from the top, and the prognosis was evaluated. We examined that stratification was possible by CTSD (**Figure 2**). Secondly, to detect the upper limit of cut-off value to stratify the prognosis by CTSD, we performed prognostic analysis using various cut-off values of CTSD (**Figure 3**). Next, we performed multivariate analysis using the Cox's proportional hazard model (**Table 1**) and examined whether the upper limit of cut-off value of CTSD could specifically stratify the prognosis in GC patients (**Figure 4**). The relationships between clinicopathological factors and CTSD were examined (**Table 2**). The S-1 intensity was calculated by dividing the dose by the specified amount. The cut off was set to 0.87, which is the average.

Statistical analysis

We performed statistical analysis using JMP version 13 for Mac (SAS Institute Inc., Cary, North Carolina, USA) and analyze the categorical variables to compare the clinicopathological features using Fisher's exact test or the Chi-square test between the two groups. RFS was calculated by the Kaplan-Meier method, and the differences between the groups were evaluated by the log lank test. The Cox's proportional hazards regression analysis was used for multivariate analysis. $P < 0.05$ was considered statistically significant.

Results

Clinicopathological features of GC patients followed by adjuvant S-1 chemotherapy

The clinicopathological features in 77 GC patients followed by S-1 after surgery were as follows. This group consisted of 48 males and 29 females with median follow-up of 1838 days (range, 949 to 2000). Of 77 patients, 24 patients were staged as pStage IIA, 23 patients as pStage IIB, 14 patients as pStage IIIA, 12 patients as pStage IIIB, and 4 patients as pStage IIIC. The 5-year RFS of the GC patients showed 78.4% and 56.3% in pStage II and pStage III, respectively, and there was significant difference according to pStage ($P = 0.008$) (data not shown). The median duration was

Table 1. Univariate and multivariate analysis for relapse free survival using the Cox's proportional hazard model

	n	Univariate[a]		Multivariate analysis[b]		
		5 yr RFS	*P*-value	HR[c]	95% CI[d]	*P*-value
Gender			0.115			
Female	29	59.7%				
Male	48	76.4%				
Age			0.652			
≥ 65	41	69.7%				
< 65	36	70.7%				
T-stage			0.043			
T4	19	47.4%				
T2/T3	58	76.8%				
N-stage			0.049			
N3	13	52.7%				
N1/N2	64	73.1%				
Venous invasion			0.198			
Present	42	62.4%				
Absent	35	79.0%				
Lymphatic invasion			0.052			
Present	55	64.5%				
Absent	22	83.9%				
Histopathological type			0.709			
Differentiated	31	73.3%				
Undifferentiated	46	67.6%				
S-1 intensity			0.608			
≥ 0.87	38	68.2%				
< 0.87	39	71.7%				
S-1 duration			0.049			
< 12 months	42	59.2%				
≥ 12 months	35	82.2%				
CTSD[e]			0.004			
< 20000 mg	36	51.9%		3.32	1.11-11.1	0.031
≥ 20000 mg	41	85.1%				

[a]Kaplan-Meier method; significance was determined by log-rank test. [b]Multivariate survival analysis was performed using Cox's proportional hazard model. [c]HR: Hazard ratio; [d]CI: Confidence interval; [e]CTSD: Cumulative total S-1 dose.

322 days (range, 3 to 1169) and the median CTSD was 20571 mg (range, 160 to 93520). The median preoperative albumin (Alb) was 4.4 g/dl (range, 2.2 to 5.3) and the median preoperative hemoglobin (HgB) was 13.5 g/dl (range, 4.6 to 18.6). No patients received neo adjuvant chemotherapy, adjuvant radiotherapy or chemo radiotherapy.

Cut-off value of CTSD to stratify the prognosis

We evenly divided CTSD into 4 groups from the top (group 1: 26640-93520 mg 19 patients, group 2: 20571-26320 mg 20 patients, group 3: 9520-20533 mg 19 patients, group 4: 160-9333 mg 19 patients), and the prognosis was evaluated (**Figure 2**). As a result, the stratification was possible by CTSD. Survival analyses were performed using various cut-off values 6000 to 20000 mg to detect the upper cut-off value for stratifying the prognosis. We demonstrated that the cut-off value of 20000 mg was the upper limit for stratifying the prognosis (*P* = 0.004, 5-year RFS; CTSD < 20000 mg vs. CTSD ≥ 20000 mg; 51.9% vs. 85.1%; **Figure 3**). In subgroup analysis by pStage II and III GC, CTSD more than 20000 mg had a poorer prognosis than CTSD less than 20000 mg (Supplementary Figure 1).

Prognostic factors for GC patients with pStage II and III followed by adjuvant S-1 chemotherapy

The significant prognostic factors were pT stage 4 (*P* = 0.043), pN stage 3 (*P* = 0.049), S-1 duration (*P* = 0.049), and CTSD less than 20000 mg (*P* = 0.004). Multivariate analysis using the Cox's proportional hazard model revealed that CTSD less than 20000 mg was an independent poor prognostic factor in pStage II and III GC followed by adjuvant S-1 chemotherapy (*P* = 0.031, HR 3.32, 95% CI 1.11-11.1; **Table 1**).

Comparison of clinicopathological factors between patients with CTSD less than 20000 mg and CTSD more than 20000 mg

The clinicopathological factors between patients with CTSD less than 20000 mg and CTSD more than 20000 mg was compared. Compared patients with CTSD more than 20000 mg, patients with CTSD less than 20000 mg had a

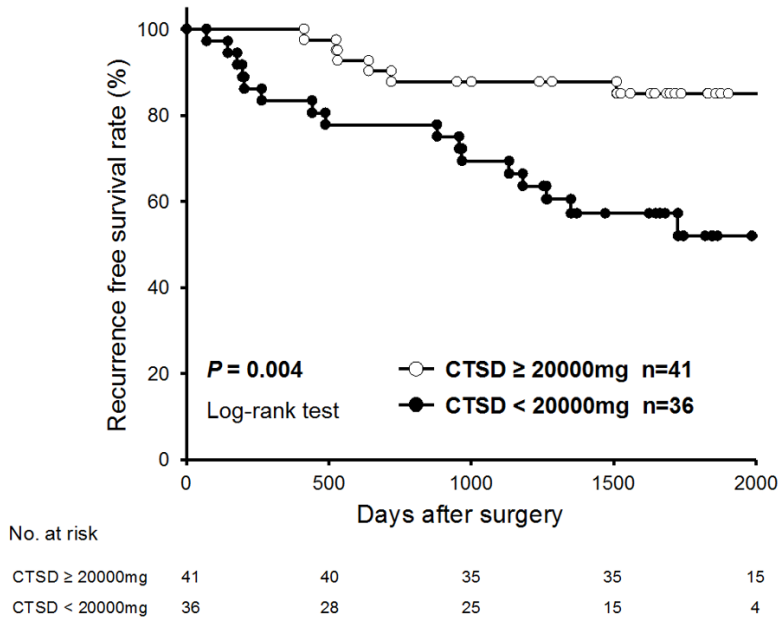


Figure 4. Relapse-free survival analysis according to 20000 mg of CTSD. The cutoff value of 20000 mg could stratify the prognosis of patients with the gastric cancer (P = 0.004, 5-year relapse free survival rate; CTSD < 20000 mg vs. CTSD ≥ 20000 mg; 51.9% vs. 85.1%).

significantly higher incidence of preoperative anemia (P = 0.041) and low nutrition (P = 0.008). Regarding the recurrence, patients with CTSD < 20000 mg had a significantly higher recurrence rate (5 year RFS; CTSD < 20000 mg vs. CTSD ≥ 20000 mg: 36% vs. 12%, P = 0.017) (**Table 2**). The rate of lymph nodes recurrence was significantly higher in the patients with CTSD less than 20000 mg than with CTSD more than 20000 mg (P = 0.019; Supplementary Table 1). In this study, peritoneal recurrence was not associated with S1 duration, intensity, or CTSD (data not shown).

Discussion

There have been only a few reports on CTSD in gastric cancer [13] and the correlation between total S-1 dose and the prognosis is unclear. In this study, we revealed that CTSD was the prognostic factor for pStage II and III GC patients followed by adjuvant chemotherapy with S-1. Moreover, this study revealed that CTSD less than 20000 mg was the poor prognostic factor. These results strongly suggest that the risk of postoperative recurrence could be reduced if S-1 was taken more than 20000 mg.

The OPAS-1 trial indicated that S-1 duration for one year, not for half year, should be recommended as standard duration for the GC patients with pStage II for adjuvant chemotherapy. This study strongly suggested the importance of S-1 duration as an adjuvant chemotherapy. However, regarding S-1 dose intensity of the OPAS-1 trial, there was 58.3% of the patients to complete eight courses and 78.3% of the patients to complete four courses [10]. Also, there was only 77.9% of the patients to continue S-1 for 6 months, 65.8% of the patients for one year in the ACTS-GC trial [9]. These results suggested that it was difficult to continue S-1 with sufficient and recommended dose intensity for one year due to side effects and other reasons. In our study, S-1 dose intensity was not proved to be a prognostic factor. As a more striking finding, S-1 duration was a prognostic factor only by univariate analysis. Multivariate analysis revealed that both S-1 dose intensity and S-1 duration were not independent prognostic factors. However, CTSD less than 20000 mg was the independent poor prognostic factor among these indicators. Thus, CTSD of 20000 mg might be the most important indicator for adjuvant S-1 chemotherapy. Also, our data suggested that it may be important to take more than 20000 mg of S-1 even if patients could not keep the recommended dose intensity and need more than one year to take more than 20000 mg of S-1.

Regarding the clinicopathological features, the patients with CTSD less than 20000 mg had a significantly higher incidence of preoperative anemia (P = 0.041) and low nutrition (P = 0.008). There was a strong correlation between preoperative anemia and low nutrition (data not shown). Previous studies revealed that preoperative low nutrition correlated to neutropenia of chemotherapy and a lower rate of completion of adjuvant chemotherapy [19, 20]. Patients with lower nutrition status may have more side effects due to immunosuppressive

Table 2. Relationships between clinicopathological factors and CTSD

Variables	n	CTSD		*P*-value[a]
		≥ 20000 mg	< 20000 mg	
Total	77	41	36	
Gender				0.497
Male	48	27 (66%)	21 (58%)	
Female	29	14 (34%)	15 (42%)	
Age				0.194
< 65	36	22 (54%)	14 (39%)	
≥ 65	41	19 (46%)	22 (61%)	
Underlying medical condition				0.612
Absent	43	24 (59%)	19 (53%)	
Present	34	17 (41%)	17 (47%)	
HgB (g/dl)				**0.041**
< 12	15	4 (10%)	11 (31%)	
≥ 12	62	37 (90%)	25 (69%)	
Alb (g/dl)				**0.008**
< 4.2	28	9 (22%)	19 (53%)	
≥ 4.2	49	32 (78%)	17 (47%)	
T-stage				0.554
T2/T3	58	32 (78%)	26 (72%)	
T4	19	9 (22%)	10 (28%)	
N-stage				0.574
N1/N2	64	35 (85%)	29 (81%)	
N3	13	6 (15%)	7 (19%)	
Complication				0.576
Absent	66	36 (88%)	30 (83%)	
Present	11	5 (12%)	6 (17%)	
Gastrectomy				0.102
Distal gastrectomy	46	28 (68%)	18 (50%)	
Total gastrectomy	31	13 (32%)	18 (50%)	
Blood loss (ml)				0.255
< 180	50	29 (71%)	21 (58%)	
≥ 180	27	12 (29%)	15 (42%)	

[a]*P* values were calculated by Chi-square or Fisher's exact test. CTSD: the cumulative total S-1 dose. NOTE: Significant values are in bold.

state, which may make it difficult to complete adjuvant chemotherapy. Therefore, for the patients with lower nutrition status, adjuvant chemotherapy may be recommended to reduce the dose so that side effects are reduced. Moreover, it is reported that S-1 monotherapy is often managed more frequently by oncologists than surgeons, including dose modifications, and could achieve higher completion rates than surgeons in patients aged 65 years and over [14]. Appropriate management, including dose modifications, of S-1 monotherapy based on patient's age and nutritional status may play an important role in prognosis. This study had several limitations. The limitations are a retrospective design and a single institution setting with a small number of patients. A Multi-institutional study or a large-scale cohort are needed.

In conclusion, CTSD less than 20000 mg was an independent poor prognostic factor. We revealed that CTSD more than 20000 mg contributed to better prognosis in pStage II and III GC.

Disclosure of conflict of interest

None.

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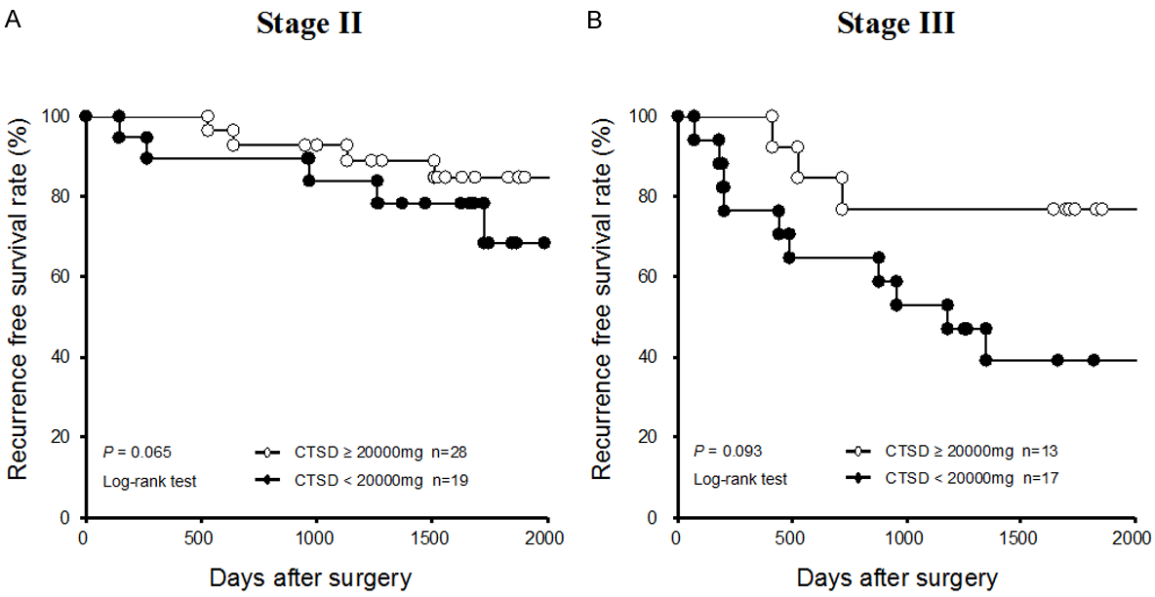

Supplementary Figure 1. Relapse-free survival analysis according to 20000 mg of CTSD. CTSD more than 20000 mg had a poorer prognosis than CTSD less than 20000 mg in subgroup analysis by pStage II and III GC.

Supplementary Table 1. Comparison of recurrence patterns according to CTSD

	n	CTSD		*P*-value[a]
		≥ 20000 mg	< 20000 mg	
Total	77	41	36	
Recurrence				**0.017**
Absent	59	36 (88%)	23 (64%)	
Present	18	5 (12%)	13 (36%)	
Peritoneal				1
Absent	69	37 (90%)	32 (89%)	
Present	8	4 (10%)	4 (11%)	
Lymph nodes				**0.019**
Absent	72	41 (100%)	31 (86%)	
Present	5	0 (0%)	5 (14%)	
Hematogenous				0.092
Absent	71	40 (98%)	31 (86%)	
Present	6	1 (2%)	5 (14%)	

[a]*P* values were calculated by Chi-square or Fisher's exact test. CTSD: Cumulative total S-1 dose. NOTE: Significant values are in bold.